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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,643	11/18/2003	Peter A. Crooks	069962-0102	2532

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,643	CROOKS ET AL.	
	Examiner	Art Unit	
	YONG S. CHONG	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9,10,13-17,28,71 and 73-85* is/are pending in the application.

4a) Of the above claim(s) *73-79 and 81-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5-7, 9-10, 13-17, 28, 71, 80, 84-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/08 has been entered.

Claim(s) 3-4, 8, 11-12, 18-27, 29-70, 72 have been cancelled. Claim(s) 84-85 have been added. Claim(s) 1-2, 5-7, 9-10, 13-17, 28, 71, 73-85 are pending. Claim(s) 73-79, 81-83 have been withdrawn. Claim(s) 1-2, 10, 15-16, 73, 78-83 have been amended. Claim(s) 1-2, 5-7, 9-10, 13-17, 28, 71, 80, 84-85 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejection of the last Office Action is maintained for reasons of record and modified below as a result of the new claim amendments.

The following new rejection will now apply.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 5-7, 9-10, 13-17, 28, 71, 80, 84-85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 12-17 of copending Application No. 11/558,782. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite a method of treating pain in a patient in need thereof comprising administering (S)-norketamine with a narcotic analgesic.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 5-7, 9-10, 13-17, 28, 71, 80, 84-85 are rejected under 35 U.S.C. 103(a) as being obvious over Harbut et al. (US Patent Application 2005/0148673 A1) in view of Ebert et al. (European Journal of Pharmacology, 333, 1997, 99-104).

The instant claims are directed to a method of treating neuropathic pain in a patient in need thereof comprising administering (S)-norketamine at a dosage of 0.01 to 8 mg/kg of body weight in conjunction with a narcotic analgesic effective to treat pain.

Harbut et al. teach treating neuropathic pain by administering a composition comprising NMDA receptor antagonist, such as ketamine (abstract), which can be co-administered with Valium (paragraph 0033). Ketamine can be administered intravenously and subcutaneously (paragraph 0038) and for a sustained period of time, such as two or more consecutive days (paragraph 0057). Oral administration is also taught by Harbut et al. (paragraph 0112). Ketamine is also disclosed to be metabolically degraded into norketamine, which is about 25% as effective as ketamine (paragraph 0081). Other pain treating drugs, such as morphine and oxycontin, were typically reduced by about 25% on the second day of treatment, while ketamine treatment continued (paragraph 0086). Typical dosage of ketamine is disclosed to be 10 mg/hour (paragraph 0100) or 240 mg per day, which meet the limitation of 0.05 to 8 mg/kg body weight or 3.5 to 560 mg for an average adult of 70 kg.

Harbut et al. teach as discussed above, however fail to specifically disclose (S)-norketamine in the dosage range of 0.05 to 8 mg/kg body weight or 3.5 to 560 mg for an average adult of 70 kg.

Ebert teaches that ketamine is taught to be a well-known NMDA receptor antagonist and has been used as an analgesic for over 30 years. In sub-anaesthetic doses the analgesic effects of ketamine are thought to be mediated by the blockade of the NMDA receptors. Norketamine is a metabolite of ketamine with similar pharmacological profiles as a NMDA receptor antagonist following an oral or i.m. dose (pg. 99-100). Therefore, norketamine has some analgesic properties. It was determined that (S)-norketamine contributes significantly to the clinical activity of (S)-ketamine (abstract). It was also determined that (S)-norketamine is approximately 8 times more potent than (R)-norketamine (pg. 102). Following oral administration of (RS)-ketamine, (S)-norketamine will be present in human plasma at sufficiently high concentrations to account for some of the observed analgesic activity. Clinical studies involving oral administration of (S)-norketamine and its reduced side effects are now being investigated in humans (pg. 103).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted (S)-norketamine in the dosage range of 0.05 to 8 mg/kg body weight or 3.5 to 560 mg for an average adult of 70 kg as disclosed by Ebert for the ketamine in the method for treating neuropathic pain as disclosed by Harbut.

A person of ordinary skill in the art would have been motivated to substitute (S)-norketamine in the dosage range of 0.05 to 8 mg/kg body weight or 3.5 to 560 mg for an average adult of 70 kg as disclosed by Ebert for the ketamine in the method for treating neuropathic pain as disclosed by Harbut because: (1) both (S)-norketamine and ketamine are functionally equivalent as NMDA receptor antagonists and as having analgesic properties; (2) ketamine breaks down metabolically to (S)-norketamine; (3) (S)-norketamine contributes significantly to the clinical activity of (S)-ketamine; and (4) (S)-norketamine is approximately 8 times more potent than (R)-norketamine. Therefore, the skilled artisan would have had a reasonable expectation of success in treating neuropathic pain by administering a composition comprising (S)-norketamine in the dosage range of 0.05 to 8 mg/kg body weight or 3.5 to 560 mg for an average adult of 70 kg. Furthermore, it is obvious to one of ordinary skill in the art to have self-administered on an outpatient basis, (S)-norketamine, to effectively treat neuropathic pain because of the convenience and ease of not having to go to the hospital as frequently and for prolonged periods of time.

Examiner notes that the dosage amounts disclosed in the rejection is inherently below a level to induce dysphoria as well as in a range of about 10 to about 20% of an amount used to induce anesthesia since a composition and its properties are inseparable. It is also obvious that a physician or medical provider would prescribe such dosages so as to limit or reduce as much side effects as possible.

"Products of identical chemical composition can not have mutual exclusive properties." Any properties exhibited by or benefits from are not given any patentable

weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to the applicant to show that the prior art product does not inherently possess the same properties as the instantly claimed product.

Response to Arguments

Applicant argues that Harbut et al. teaches away from the claimed invention. Since (S)-norketamine is not mentioned at all in Harbut et al., why would one of ordinary skill in the art actually replace ketamine with norketamine, let alone (S)-norketamine?

This is not persuasive because Applicant has misinterpreted the Harbut et al. reference. There is no mention of norketamine being ineffective in treating pain nor is there any mention of the conversion of ketamine to norketamine as undesirable. In fact, Harbut et al. clearly states that norketamine is 25% as effective in treating pain when compared to ketamine. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in treating pain by administering norketamine. The fact that norketamine may be less effective than ketamine matters little since the prior art clearly teaches that norketamine is used to treat pain.

In response to applicant's arguments against the references, one cannot show nonobviousness by attacking references individually where the rejections are based on

the combination of references. See *In re Keller*, 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue against the Ebert reference is limited to in vitro work only and that in vivo correlation is merely a product of predictions and wishful thinking. More specifically, the authors use the terms "potent" and "potency" as a relative strength or weakness of the compounds tested in terms of binding to receptor molecules present in vitro assays. As Applicants are aware, one cannot confidently draw a direct correlation between the results of these in vitro binding assays and the actual potency of the same compounds to illicit a physiological or pharmacological response in an in vivo setting.

This is not persuasive because Applicant misses the point of using the Ebert reference in the rejection. The issue of whether there is a sound correlation between the in vitro results and in an in vivo setting is irrelevant because Harbut et al. already has clearly shown norketamine as being useful in treating pain in humans. The Ebert reference was used to merely show that (S)-norketamine is approximately 8 times more potent than (R)-norketamine. Therefore, based on this result, the following calculation is submitted:

Harbut teaches administration of ketamine at 10 mg/hr, which translates to 240 mg over a 24 hour period.

Since norketamine is 25% as effective as ketamine, an equipotent dosage for norketamine would calculate to 240 mg x 4 = 960 mg.

The claimed dosage range for (S)-norketamine is 3.5 to 560 mg for an average adult of 70 kg.

What is the motivation for reducing the dosage from 960 mg to 560 mg for (S)-norketamine?

Ebert teaches that (S)-norketamine is approximately 8 times more potent than (R)-norketamine, therefore (S)-norketamine can be used in a much reduced dosage than (R)-norketamine or racemic norketamine.

It is submitted that going from 960 mg to 560 mg for the dosage of (S)-norketamine is well within the optimization and routine experimentation of the skilled artisan in view of the fact that (S)-norketamine is approximately 8 times more potent than (R)-norketamine or racemic norketamine.

Applicant argues unexpected results in the Kleven Declaration, particularly Exhibit 1, which shows (S)-norketamine, given at equipotent dosage, results in an unexpected reduction of side effects in comparison to an equipotent dosage of racemic ketamine.

This is not persuasive because the Kleven Declaration is not commensurate with the scope of the claims. Applicant is reminded that the instant claims recite administration of (S)-norketamine at a dosage of 0.01 to 8 mg/kg, while the data in the Kleven Declaration is drawn from administering (S)-norketamine at a dosage of 16 mg/kg. Furthermore, a fair comparison cannot be drawn to ketamine, since it was adminstered at a different dosage of 8 mg/kg. Applicant is requested to compare (S)-

norketamine and ketamine at the same dosage, which falls within the claimed dosage range, and using the same number of rats.

Nonetheless, Examiner still stands by the previous assertion that the claimed unexpected reduction of side effects is incorrect because this property is known in the prior art, therefore considered to be expected. In fact, the cited prior art reference above, Ebert, teaches that clinical studies involving oral administration of (S)-norketamine are accompanied with reduced side effects in humans. Applicant is reminded that (S)-norketamine is already known for its reduced side effects, therefore the Kleven Declaration shows nothing unexpected.

Applicant's arguments directed to the claim amendment regarding the upper dosage limit and bioavailability of drugs administered orally are addressed above and in the modified obviousness rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/YONG S. CHONG/
Primary Examiner, Art Unit 1617

YSC